DOCKET NO.: 205559US0PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Paolo PEVARELLO, et al.

SERIAL NO.: NEW U.S. PCT APPLICATION

FILED: HEREWITH

INTERNATIONAL APPLICATION NO.: PCT/EP99/08307

INTERNATIONAL FILING DATE: 27 OCTOBER 1999

FOR: 2-UREIDO-THIAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS ANTITUMOR AGENTS

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119 AND THE INTERNATIONAL CONVENTION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

COUNTRY	APPLICATION NO.	DAY/MONTH/YEAR
GREAT BRITAIN	9823873.6	30 OCTOBER 1998

A certified copy of the corresponding Convention application(s) was submitted to the International Bureau in PCT Application No. **PCT/EP99/08307.** Receipt of the certified copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

Respectfully submitted,
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EP99/ 8307

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Signed A.W. Brewer.

Dated 2 August 1999

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02NOV98 E401579-2 D00192
P01/7700 0.00 - 9823873.6

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form))

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — P.75596 GCW.CMK

2. Patent application number *(The Patent Office will fill in this part)* — 9823873.6 — OCT 1998

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — Pharmacia & Upjohn S.p.A.
Via Robert Koch 1.2
20152 Milan, Italy

Patents ADP number *(if you know it)* — 7100001001

If the applicant is a corporate body, give the country/state of its incorporation — Italy

4. Title of the invention — 2-UREIDO-THIAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS ANTITUMOUR AGENTS

5. Name of your agent *(if you have one)* — J A KEMP & CO

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — 14 SOUTH SQUARE
GRAY'S INN
LONDON WC1R 5LX

Patents ADP number *(if you know it)* — 26001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer "Yes" if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body:
See note (d)) — Yes

Patents Form 1/77

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Continuation sheets of this form	
Description	22
Claim(s)	7
Abstract	1
Drawing(s)	

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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	2 x 7
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature JAKemp&6 Date 30 October 1998

12. Name and daytime telephone number of person to contact in the United Kingdom

C M KEEN
0171 405 3292

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FC 858/5

2-UREIDO-THIAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS ANTITUMOR AGENTS

The present invention relates to 2-ureido-thiazole derivatives and, more in particular, it relates to 2-ureido-1,3-thiazoles, to a process for their preparation, to pharmaceutical compositions containing them and to their use as antitumor agents.

Several cytotoxic drugs such as, e.g. fluorouracil (5-FU), doxorubicin and camptothecins result to damage DNA or to affect cellular methabolic pathways and thus cause, in many cases, an indirect block of the cell cycle.
Therefore, by producing an irreversible damage to both normal and tumor cells, these agents result in a significant toxicity and side-effects.
In this respect, compounds capable of being highly specific antitumor agents by selectively leading to tumor cell arrest and apoptosis, with comparable efficacy but reduced toxicity than the currently available drugs, are desirable.

It is well known in the art that progression through the cell cycle is governed by a series of checkpoint controls, otherwise referred to as restriction points, which are regulated by a family of enzymes known as the cyclin-dependent kinases (cdk).
In their turn the cdks themselves are regulated at many levels such as, for instance, binding to cyclins.
For a general reference to cyclins and cyclin-dependent kinases see, for instance, Kevin R. Webster et al. in Exp. Opin. Invest. Drugs, 1998, Vol. 7(6), 865-887.
Checkpoint controls are defective in tumor cells due, in part, to disregulation of cdk activity. For example, altered expression of cyclin E and cdk's has been observed in tumor cells, and deletion of the cdk inhibitor p27 KIP gene in mice has been shown to result in a higher incidence of cancer.

Increasing evidence supports the idea that the cdks are rate-limiting enzymes in cell cycle progression and, as such, represent molecular targets for therapeutic intervention. In particular, the direct inhibition of cdk/cyclin kinase activity should be helpful in restricting the unregulated proliferation of a tumor cell.

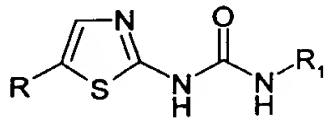
It has now been found that the compounds of the invention, hereinafter referred to as 2-ureido-1,3-thiazole derivatives, are endowed with cdk/cyclin kinase inhibitory activity and are thus useful in therapy as antitumor agents whilst lacking, in terms of both toxicity and side effects, the aforementioned drawbacks known for currently available antitumor drugs.
In addition, besides of being useful in the treatment of cancer, these 2-ureido-1,3-thiazole derivatives are also useful in the treatment of a variety of other cell proliferative disorders such as, for instance, psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis, and in the treatment of Alzheimer's disease.

Several 2-ureido-1,3-thiazole derivatives are known in the art.
Just few examples among them are N-methyl-N'-(5-chloro-2-thiazolyl)-urea, described as synthetic intermediate for preparing herbicides in US 3,726,891 (Shell Co.); N-methyl- and N-ethyl-N'-(5-chloro-2-thiazolyl)-urea, both described as herbicides in Chemical Abstracts (1975) 83:114381.
Other 2-ureido-1,3-thiazole derivatives have been described in the art as therapeutic agents.
Among them are N-methyl- and N-phenyl-N'-(5-chloro-2-thiazolyl)-urea which have been described as sedative and antiinflammatory agents in FR M. 7428 (Melle-bezons) or N-[4-(5-oxazolyl)phenyl]-N'-(5-methyl-2-thiazolyl)-urea, described as inosine 5'-monophosphate dehydrogenase

inhibitor (IMPDH) in WO 97/40028 (Vertex Pharmaceuticals Inc.).

To the extent of our knowledge, however, none of these known compounds has been reported as antitumor agent or, even more, as cell cycle inhibitor.

Accordingly, the present invention provides the use of a compound which is a 2-ureido-1,3-thiazole derivative of formula (I)



(I)

wherein

R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C_3-C_6 cycloalkyl and straight or branched C_1-C_6 alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy grouops, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

R_1 is a straight or branched C_1-C_6 alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for treating cell proliferative disorders or Alzheimer's disease.

In the present description, unless otherwise specified, with the term halogen atom we intend a fluorine, chlorine, bromine or iodine atom, chlorine and bromine being preferred.

Both alkyl and alkoxy as used herein stand for C_1-C_6 alkyl and C_1-C_6 alkoxy groups. With the term straight or branched C_1-C_6 alkyl or C_1-C_6 alkoxy group we intend a group selected from, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy or the like.

The term aryl typically stands for phenyl or for an optionally benzocondensed 5 or 6 membered aromatic heterocyclic with 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur.

With the term C_3-C_6 cycloalkyl group we intend a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group, cyclopropyl being preferred.

With the term 5 or 6 membered aromatic heterocycle with 1 or 2 heteroatoms selected among nitrogen, oxygen and sulphur, pyrrole, furan, thiophene, imidazole, pyrazole, thiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine or the like, are intended.

Pharmaceutically acceptable salts of the compounds of formula (I) are the acid addition salts with inorganic or organic, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric, phosphoric, acetic, trifluoroacetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulfonic, isethionic and salicylic acid, as well as the salts with inorganic or organic bases, e.g. alkali or alkaline-earth metals, especially sodium, potassium, calcium or magnesium hydroxides, carbonates or bicarbonates, acyclic or cyclic

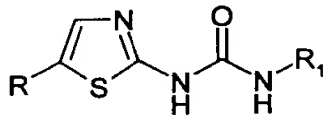
amines, preferably methylamine, ethylamine, diethylamine, triethylamine or piperidine.

The compounds of formula (I) may have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers.

Accordingly, the use as an antitumor agent of all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I) are also within the scope of the present invention.

As above reported, some of the compounds of formula (I) of the invention have been reported in the art as useful therapeutic agents, for instance as sedative, antiinflammatory or IMPDH inhibitors but not as antitumor agents or even cell cycle inhibitors.

Therefore, it is a further object of the present invention a compound which is a 2-ureido-1,3-thiazole derivative of formula (Ia)



(Ia)

wherein

R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C_3-C_6 cycloalkyl and straight or branched C_1-C_6 alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro,

alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

R_1 is a straight or branched C_1-C_6 alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

or a pharmaceutically acceptable salt thereof, for use as a medicament;

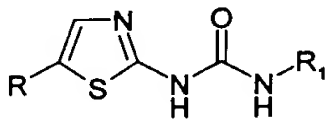
provided that:

a) when R is a chlorine atom then R_1 is not methyl or phenyl; and

b) when R is methyl then R_1 is not 4-(5-oxazolyl)phenyl.

Among the compounds of formula (I) above reported, several 2-ureido-1,3-thiazole derivatives result to be novel compounds.

Therefore, the present invention further provides a compound which is a 2-ureido-1,3-thiazole derivative of formula (Ib)



(Ib)

wherein

R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C_3-C_6 cycloalkyl and straight or branched C_1-C_6 alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulfonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or

substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulphonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

R_1 is a straight or branched C_1-C_6 alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

or a pharmaceutically acceptable salt thereof;

provided that:

a') when R is a chlorine or bromine atom then R_1 is not C_1-C_3 alkyl or phenyl;

b') when R is methyl then R_1 is not methyl, phenyl or 4-(5-oxazolyl)phenyl; and

c') when R is phenyl then R_1 is not chlorophenyl.

From the foregoing it is clear to the man skilled in the art that the novel compounds of the invention of formula (Ib) are within the meanings of the compounds of general formula (Ia) which, in turn, are within the meanings of the compounds of formula (I).

Preferred compounds of the invention of formula (Ib), and thus of formula (Ia) and (I), are the compounds wherein R is a halogen atom, a straight or branched C_1-C_4 alkyl group, a phenyl or cycloalkyl group, and R_1 is an unsubstituted or substituted phenyl, phenylalkyl or is a 5 or 6 membered aromatic heterocycle with one heteroatom selected among nitrogen, oxygen and sulphur.

Still more preferred compounds, within this class, are the compounds of formula (Ib) wherein R is a bromine atom, a straight or branched C_1-C_3 alkyl group, a phenyl or cyclopropyl group, and R_1 is an ~~which is~~ unsubstituted or substituted phenyl group, a phenylalkyl or a heterocycle selected from pyridine and benzothiophene.

Examples of preferred compounds for use in the invention, whenever appropriate in the form of pharmaceutically acceptable salts, are the following:

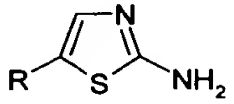
1-(5-isopropyl-1,3-thiazol-2-yl)-3-phenyl-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-phenyl-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-phenyl-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-phenyl-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;

1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-benzyl-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-benzyl-urea;

1-(5-phenyl-1,3-thiazol-2-yl)-3-benzyl-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-benzyl-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(benzothiophenyl-2-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(benzothiophenyl-2-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(benzothiphenyl-2-yl)-urea;
and
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(benzothiphenyl-2-yl)-urea

The compounds of formula (Ib) object of the present invention and the salts thereof can be obtained, for instance, by a process comprising:

a) reacting a compound of formula (II)



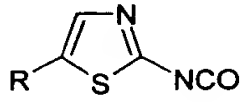
(II)

wherein R is as defined above, with a compound of formula (III)

R_1—NCO (III)

wherein R_1 is as defined above; or

b) reacting a compound of formula (IV)



(IV)

wherein R is as defined above, with a compound of formula (V)

$$R_1-NH_2 \quad (V)$$

wherein R_1 is as defined above;

and, if desired, converting a 2-ureido-1,3-thiazole derivative of formula (Ib) into another such derivative of formula (Ib), and/or into a salt thereof.

It is clear to the man skilled in the art that if the compound of formula (Ib), prepared according to the above processes a) or b), is obtained as an admixture of isomers, their separation into the single isomers of formula (Ib) according to conventional techniques is still within the scope of the present invention.

Likewise, the conversion into the free 2-ureido-1,3-thiazole derivative (Ib) of a corresponding salt thereof, according to well-known procedures in the art, is still within the scope of the invention.

The above process-variants a) and b) are analogy processes which can be carried out according to well known methods.

The reaction between a compound of formula (II) and a compound of formula (III) as defined under process a), or the reaction between a compound of formula (IV) and a compound of formula (V) as defined under process b), can be carried out in a suitable solvent such as, for instance, dichloromethane, chloroform, tetrahydrofuran, diethyl ether, 1,4-dioxane, acetonitrile, toluene or acetone, at a temperature ranging from room temperature to reflux for a time varying between about 1 to 96 hours.

Also the optional conversion of a compound of formula (Ib) into another compound of formula (Ib) can be carried out according to known methods.

As an example, the nitro group of a compound of formula (Ib) may be converted into an amino group by treatment, for example, with stannous chloride in concentrated hydrochloric acid and by using, if necessary, an organic solvent such as acetic acid, 1,4-dioxane and

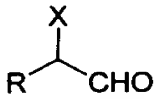
tetrahydrofuran, at a temperature varying between room temperature and about 100°C.

Likewise, an alkylthio or an arylthio group may be converted into the corresponding alkylsulfonyl and arylsulfonyl group by reaction, for example, with m-chloroperbenzoic acid in a suitable solvent such as dichloromethane or chloroform, at a temperature varying between about -5°C and room temperature.

The optional salification of a compound of formula (Ib) or the conversion of a salt into the free compound as well as the separation of a mixture of isomers into the single isomers may be carried out by conventional methods.

The compounds of formula (II) and (IV) according to processes a) and b) are known compounds or can be obtained according to known methods.

For example, a compound of formula (II) wherein R is as defined above can be obtained by reacting a compound of formula (VI)



(VI)

wherein X is a bromine or chlorine atom, with thiourea in a suitable solvent such as methanol, ethanol, tetrahydrofuran, 1,4-dioxane or toluene, at a temperature varying between room temperature and reflux, for a suitable time ranging from about 1 hour to about 24 hours.

A compound of formula (IV) can be obtained, for instance, by reacting a compound of formula (II) wherein R is as defined above with bis(trichloromethyl) carbonate or trichloromethyl chloroformate in the presence, if necessary, of a tertiary base such as triethylamine, N,N-diisopropylethylamine or pyridine, in a suitable solvent such as dichloromethane, chloroform or toluene, at a temperature ranging from about -20°C to reflux.

The compounds of formula (III), (V) and (VI) are well-known commercially available compounds or, alternatively, may be conventionally prepared according to known methods in organic chemistry.

When preparing the compounds of formula (Ib) according to the process object of the present invention, optional functional groups within both the starting materials or the intermediates thereof, which could give rise to unwanted side reactions, need to be properly protected according to conventional techniques.
Likewise, the conversion of these latter into the free deprotected compounds may be carried out according to known procedures.

It is further clear to the man skilled in the art that the above process according to variants a) and b) for preparing the compounds of formula (Ib) can be applied as well to the preparation of the compounds of formula (I) and (Ia) which also include known compounds.

Pharmacology

The compounds of formula (I), also encompassing those of formula (Ia) and (Ib), are active as cdk/cyclin inhibitors as they gave positive results when tested according to the following procedure.
The compounds of formula (I) are therefore useful to restrict the unregulated proliferation of tumor cells, hence in therapy in the treatment of various tumors such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.
In addition, the compounds of formula (I) are also useful in the treatment of other cell proliferative disorders such as psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis and in the treatment of Alzheimer's disease.

The inhibiting activity of putative cdk/cyclin inhibitors and the potency of selected compounds was determined through a method of assay based on the use of the

MultiScreen-PH 96 well plate (Millipore), in which a phosphocellulose filter paper was placed at each well bottom allowing binding of positive charged substrate after a washing/filtration step.

When a radioactivity labelled phosphate moiety was transferred by the ser/threo kinase to the filter-bound histone, light emitted was measured in a scintillation counter.

The inhibition assay of cdk2/Cyclin A activity was performed according to the following protocol:

Kinase reaction: 1.5 µM histone H1 substrate, 25 µM ATP (0.5 uCi P^{33}g-ATP), 100 ng Cyclin A/cdk2 complex, 10 µM inhibitor in a final volume of 100 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT) were added to each well of a 96 U bottom well plate. After 10 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 100 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labelled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Results: data were analysed and expressed as % inhibition referred to total activity of enzyme (=100%).

All compounds showing inhibition ≥ 50 % were further analysed in order to study and define the kinetic-profile of inhibitor through Ki calculation.

The protocol used was the same described above, except for ATP and substrate concentrations. Either the concentration

of ATP and histone H1 substrate were varied: 4, 8,12, 24, 48 μM for ATP (containing proportionally diluted $P^{33}g$-ATP) and 0.4, 0.8, 1.2, 2.4, 4.8 μM for histone were used in absence and presence of two different, properly chosen inhibitor concentrations.
Experimental data were analysed by the computer program SigmaPlot for Ki determination, using a random bireactant system equation:

$$v = \frac{Vmax \quad \frac{(A)(B)}{aK_AK_B}}{1 + \frac{(A)}{K_A} + \frac{(B)}{K_B} + \frac{(A)(B)}{aK_AK_B}}$$

where A=ATP and B=histone H1.

The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g. to humans, can be administered by the usual routes and the dosage level depends upon the age, weight, conditions of the patient and the administration route.
For example, a suitable dosage adopted for oral administration of a compound of formula (I) may range from about 10 to about 500 mg pro dose, from 1 to 5 times daily.
The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous and/or intrathecal and/or intraspinal injection or infusion.

The present invention also includes pharmaceutical compositions comprising a compound of formula (Ia), thus encompassing those of formula (Ib), or a pharmaceutically acceptable salt thereof in association with a

pharmaceutically acceptable excipient (which can be a carrier or a diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatine, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusions may contain as carrier, for example, sterile

water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions or they may contain as a carrier propylene glycol.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the present invention.

Example 1

Preparation of methyl cyclopropylacetate

Cyclopropylacetic acid (1.08 g; 10.57 mmol) was dissolved in 50 ml of methanol. The solution was cooled to 0°C and 5 ml of sulfuric acid 96% were dropped under stirring. The solution was maintained at room temperature overnight and then poured onto ice-water, basified with 30 % ammonium hydrate and finally extracted with methylene chloride. The organic layer was dried over sodium sulfate and evaporated to dryness to give 1.1 g of an oily product (90% yield) which was used as such without any further purification.

Example 2

Preparation of 2-cyclopropylethanol

Sodium (85 mg; 0.004 mmol) was dissolved in 50 ml of methanol and 8.7 g (0.23 mol) of sodium borohydride were added. A solution of 3.7 g (0.032 mol) of methyl cyclopropylacetate, prepared according to example 1, in 20 ml of methanol was dropped to the mixture under stirring. The reaction was maintained at reflux for 6 hours, then 300 ml of brine were added and the crude extracted with methylene chloride.

The organic layer was dried over sodium sulfate and evaporated to dryness to give 1.52 g (55% yield) of the title compound.

Example 3

Preparation of a compound of formula (VI): 2-cyclopropylethanal

Oxalyl chloride (1.24 ml; 14.18 mmol) was dissolved in 10 ml of methylene chloride; after cooling to -60°C a solution of 1.02 g (11.9 mmol) of 2-cyclopropylethanol, prepared according to example 2, in 10 ml of methylene chloride was added dropwise. The mixture was maintained under stirring for 30 minutes at the same temperature, then 8.3 ml (59.5 mmol) of triethylamine were added.

After 2 hours at 0°C water was added. The mixture was diluted with methylene chloride and washed successively with 1M hydrochloric acid, water, saturated sodium bicarbonate and finally with brine. The organic layer was dried over sodium sulfate and evaporated to dryness to give 0.31 g (30% yield) of the title compound.

Example 4

Preparation of a compound of formula (II): 2-amino-5-isopropyl-1,3-thiazole

3-Methylbutanaldehyde (2 ml; 18.6 mmol) was dissolved in 15 ml of dioxane.

A solution 2% v/v of bromine in dioxane (40.4 ml; 18.6 mmol) was dropped therein at 0°C. The mixture was maintained at room temperature under stirring for 2 hours, then 2.83 g (37.2 mmol) of thiourea and 5 ml of ethanol were added. After 6 hours at room temperature the solution was evaporated to dryness, the residue was dissolved in methylene chloride and the product extracted with 1M hydrochloric acid; the aqueous layer was made basic by using 30% ammonium hydrate and extracted again with methylene chloride.

The organic phase was dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on a silica gel column, eluting with cyclohexane-ethylacetate to give 1.1 g (42% yield) of the title compound.

^{1}H-NMR (DMSO-d^6) δ ppm: 6.6 (s, 2H, NH_2); 6.58 (s, 1H, thiazole CH); 2.9 (m, 1H, $\underline{CH}Me_2$); 1.18 (s, 3H, $\underline{Me}CHMe$); 1.17 (s, 3H, $MeCH\underline{Me}$).

By analogous procedures the following compounds can be prepared:
2-amino-5-phenyl-1,3-thiazole; and
2-amino-5-cyclopropyl-1,3-thiazole.

Example 5

Preparation of a compound of formula (I): 1-(5-bromo-1,3-thiazol-2-yl)-3-phenyl-urea

Phenylisocyanate (1.7 ml; 15.6 mmol) was added to a solution of 2-amino-5-bromo-1,3-thiazole hydrobromide (4 g; 15.6 mmol) and triethylamine (2.1 ml; 15.6 mmol) in dichloromethane (70 ml), maintained under magnetic stirring at room temperature. After about 4 days, methanol (7 ml) was added and the reaction mixture was then washed with brine, dried over sodium sulfate and evaporated.
The residue was purified by chromatography on silica gel (dichloromethane and then dichloromethane/methanol=90:10) to give 1.9 g (52%) of the title compound as a colourless solid (m.p. 166-169°C/dec.).
^{1}H-NMR ($CDCl_3$) δ ppm: 10.50 (bs, 1H, -NHCONHPh); 8.50 (bs, 1H, -NHCONHPh);7.45 (d, J = 7.6 Hz, 2H, o-Ph hydrogens); 7.36 (dd, J = 7.3 and 7.6 Hz, 2H, m-Ph hydrogens); 7.29 (s, 1H, thiazole CH); 7.16 (t, J = 7.3 Hz, 1H, p-Ph hydrogens).

By analogous procedure, and by starting from the corresponding isocyanate, the following compounds can be prepared:
1-(5-phenyl-1,3-thiazol-2-yl)-3-phenyl-urea
^{1}H-NMR (DMSO-d^6) δ ppm: 10.56 (bs, 1H, -NHCONHPh); 8.99 (bs, 1H, NHCONHPh); 7.77 (s, 1H, thiazole CH); 7.6-7.0 (m, 10H, phenyl);
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea;

1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea

m.p.>200°C

^{1}H-NMR (DMSO-d^6) δ ppm: 10.58 (bs, 1H, -NHCONHPh); 9.38 (bs, 1H NHCONHPh); 7.75 (d, 2H, H3 and H5 Ph); 7.61 (d, 2H, H2 and H6 Ph); 7.21 (s, 2H, SO_2NH_2); 7.02 (s, 1H, thiazole CH); 3.02 (m, 1H, CH(Me)$_2$); 1.22 (s, 3H, MeCHMe); 1.21 (s, 3H, MeCHMe);

1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea;

1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea;

1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea

m.p. 149-150°C;

1-(5-bromo-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea

m.p. 190-191°C;

1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea;

1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea;

1-(5-isopropyl-1,3-thiazol-2-yl)-3-phenyl-urea;

1-(5-phenyl-1,3-thiazol-2-yl)-3-phenyl-urea;

1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-phenyl-urea;

1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;

1-(5-bromo-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;

1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;

1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;

1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;

1-(5-bromo-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;

1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;

1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;

1-(5-isopropyl-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;

1-(5-bromo-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;

1-(5-phenyl-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;

1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;

1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;

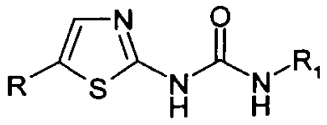
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;

1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;

1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-benzyl-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-benzyl-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-benzyl-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-benzyl-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(benzothiophen-2-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(benzothiophen-2-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(benzothiophen-2-yl)-urea; and
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(benzothiophen-2-yl)-urea.

CLAIMS

1. The use of a compound which is a 2-ureido-1,3-thiazole derivative of formula (I)



(I)

wherein

R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C_3-C_6 cycloalkyl and straight or branched C_1-C_6 alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

R_1 is a straight or branched C_1-C_6 alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

or a pharmaceutically acceptable salt thereof;

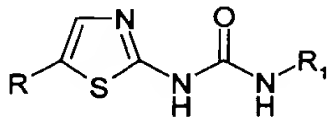
in the manufacture of a medicament for treating cell proliferative disorders or Alzheimer's disease.

2. Use according to claim 1 wherein the medicament is for treating tumors.

3. Use according to claim 2 wherein the medicament is an antitumour medicament which enables either cell cycle inhibition or cdk/cyclin kinase inhibition.

4. Use according to claim 1 wherein the medicament is for treating psoriasis or vascular smooth cell proliferation.

5. A compound which is a 2-ureido-1,3-thiazole derivative of formula (Ia)



(Ia)

wherein

R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C_3-C_6 cycloalkyl and straight or branched C_1-C_6 alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulfonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulphonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

R_1 is a straight or branched C_1-C_6 alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

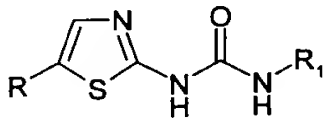
or a pharmaceutically acceptable salt thereof, for use as a medicament;

provided that:

a) when R is a chlorine atom then R_1 is not methyl or phenyl; and

b) when R is methyl then R_1 is not 4-(5-oxazolyl)phenyl.

6. A compound which is a 2-ureido-1,3-thiazole derivative of formula (Ib)



(Ib)

wherein

R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C_3-C_6 cycloalkyl and straight or branched C_1-C_6 alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

R_1 is a straight or branched C_1-C_6 alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

or a pharmaceutically acceptable salt thereof;

provided that:

a') when R is a chlorine or bromine atom then R_1 is not C_1-C_3 alkyl or phenyl;

b') when R is methyl then R_1 is not methyl, phenyl or 4-(5-oxazolyl)phenyl; and

c') when R is phenyl then R_1 is not chlorophenyl.

7. A compound according to claim 6 wherein R is a halogen atom, a straight or branched C_1-C_4 alkyl group, a phenyl or cycloalkyl group, and R_1 is an unsubstituted or substituted phenyl, phenylalkyl or is a 5 or 6 membered aromatic heterocycle with one heteroatom selected from nitrogen, oxygen and sulphur.

8. A compound according to claim 7 wherein R is a bromine atom, a straight or branched C_1-C_3 alkyl group, a phenyl or cyclopropyl group, and R_1 is an unsubstituted or substituted phenyl group, a phenylalkyl or a heterocycle selected from pyridine and benzothiophene.

9. A use according to claim 1 or a compound as claimed in claim 5 or claim 6, wherein the 2-ureido-1,3-thiazole derivative is selected from:

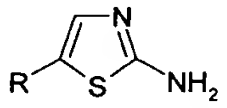
1-(5-isopropyl-1,3-thiazol-2-yl)-3-phenyl-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-phenyl-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-phenyl-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-phenyl-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-sulfamoyl-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-methoxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;

1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-chloro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-chloro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(2-chloro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-methoxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-hydroxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-hydroxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(2-methoxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(2-hydroxy-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;

1-(5-bromo-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-nitro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(4-amino-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-nitro-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(3-amino-phenyl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-benzyl-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-benzyl-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-benzyl-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-benzyl-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(pyrid-3-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(pyrid-4-yl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(pyrid-2-yl)-urea;
1-(5-isopropyl-1,3-thiazol-2-yl)-3-(benzothiophen-2-yl)-urea;
1-(5-bromo-1,3-thiazol-2-yl)-3-(benzothiophen-2-yl)-urea;
1-(5-phenyl-1,3-thiazol-2-yl)-3-(benzothiophen-2-yl)-urea;
1-(5-cyclopropyl-1,3-thiazol-2-yl)-3-(benzothiophen-2-yl)-urea.

10. A process for producing a compound as defined in claim 6, which process comprises:

a) reacting a compound of formula (II)



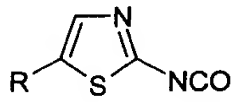
(II)

with a compound of formula (III)

R_1—NCO (III)

wherein R and R_1 have the meanings reported in claim 5; or

b) reacting a compound of formula (IV)



(IV)

with a compound of formula (V)

R_1—NH_2 (V)

wherein R and R_1 are as defined in claim 6;

and, if desired, converting a 2-ureido-1,3-thiazole derivative of formula (Ib) into another such derivative of formula (Ib), and/or into a pharmaceutically acceptable salt thereof.

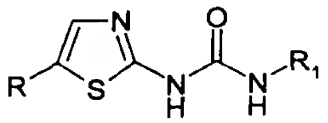
11. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers and/or diluents and, as the active principle, an effective amount of a compound as defined in claim 5 or 6.

12. Use of a compound as defined in claim 5 or 6 for the manufacture of an antitumor medicament which enables either cell cycle inhibition or cdk/cyclin kinase inhibition.

ABSTRACT

2-UREIDO-THIAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS ANTITUMOUR AGENTS

Compounds which are 2-Ureido-1,3-thiazole derivatives of formula (I)



(I)

wherein R is a halogen atom or is selected nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C_3-C_6 cycloalkyl and straight or branched C_1-C_6 alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

R_1 is a straight or branched C_1-C_6 alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R, or pharmaceutically acceptable salts thereof, are useful for treating cell proliferative disorders and Alzheimer's disease.